# BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

## IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10375 A2

(51) International Patent Classification[7]: A61H

(21) International Application Number: PCT/IL00/00467

(22) International Filing Date: 3 August 2000 (03.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/368,124 4 August 1999 (04.08.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/368,124 (CIP)
Filed on 4 August 1999 (04.08.1999)

(71) Applicant *(for all designated States except US)*: **IMPULSE DYNAMICS NV** [NL/NL]; 3 L.B. Smithplein, Curacao (AN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FELSEN, Bella** [IL/IL]; Hatzvi Street 26, 34355 Haifa (IL). **DARVISH, Nissim** [IL/IL]; Hantke Street 22A, 34606 Haifa (IL). **GOLDENHOLZ, Daniel** [US/US]; 2231 W. Glenbrook Lane, Mequon, WI 53092 (US).

(74) Agents: **COLB, Sanford, T. et al.**; Sanford T. Colb & Co., P.O. Box 2273, 76122 Rehovot (IL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *Without international search report and to be republished upon receipt of that report.*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 01/10375 A2

(54) Title: INHIBITION OF ACTION POTENTIALS

(57) Abstract: Apparatus (20) for modifying the electrical behavior of nervous tissue (30) in a human subject is provided. At least one inhibiting electrode (22) is placed in a vicinity of the subject's nervous tissue, and a control unit (40) drives the at least one inhibiting electrode to apply electrical energy to the nervous tissue to inhibit propagation therein of an action potential. Preferably, application of the electrical energy substantially does not cause generation of an action potential in at least a portion of the nervous tissue.

# INHIBITION OF ACTION POTENTIALS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of US Patent Application 09/368,124, filed August 4, 1999, entitled, "Inhibition of action potentials," which is assigned to the assignee of the present patent application and is incorporated herein by reference.

## FIELD OF THE INVENTION

The present invention relates generally to control of electrophysiological behavior, and specifically to electrically-mediated inhibition of action potentials.

## BACKGROUND OF THE INVENTION

In the central and peripheral nervous systems, action potentials are generated by nerve cells and transmitted by axons. In the normal physiological state, the presence, absence, and repetition rate of an action potential may convey useful information from a source nerve cell to a target nerve cell. In the human brain, the well-orchestrated interactions of approximately one hundred billion neurons, each neuron connected to an average of ten thousand other neurons, enables the sophisticated command, control and communication abilities associated with humans. In the peripheral nervous system, afferent nerve fibers transmit action potentials, which are responsive to the outputs of sensory nerves, while efferent nerve fibers control muscle tissue and glands.

In the pathological state, action potentials are transmitted which do not serve a useful purpose, and may cause discomfort, pain, or death. Pain, in many cases, has a positive effect, because it prevents the person in pain from further injuring damaged tissue. However, various types of pain, such as chronic low back or wrist pain, and phantom limb pain following amputation, do not necessarily help the person's overall condition, and can cause severe distress.

During various medical procedures, an anesthetic is given to a patient to block the perception of pain that would otherwise be felt. In local anesthesia, the transmission of nerve signals to the brain is inhibited, while in general anesthesia, a state of unconsciousness is induced. Both local and general anesthesia have complications, which

may include allergic reactions, liver failure, kidney damage, bleeding, blood clots, loss of limb function, paralysis, and, occasionally, death.

Defibrillation of a fibrillating heart is a life-saving treatment, in which the heart is stimulated with a high voltage that restores standard cardiac rhythm. It is a painful procedure, and sometimes unnecessarily painful when an implanted automatic defibrillator fires inappropriately.

Epilepsy is a chronic disorder characterized by paroxysmal brain dysfunction due to excessive neuronal discharge, and is usually associated with some alteration of consciousness. Drug treatments for epilepsy are widespread, but are generally viewed as not fully satisfactory. Surgical treatments often involve the removal of brain tissue, and pose significant risk to the patient.

In an article entitled, "Vagus nerve stimulator," in *Medical Sciences Bulletin*, September, 1997, which is incorporated herein by reference, a method of vagus nerve stimulation is described for treating seizures. The article notes two processes which may be initiated by the stimulation: changing of electrical thresholds and/or decreasing of the quantity of stimulatory neurotransmitters. Side effects reported with use of the stimulation technique include the induction of seizures in 20% of the treated patients.

An article by Shoogo Ueno, entitled "Biomagnetic approaches to studying the brain," in *IEEE Engineering in Medicine and Biology*, May/June, 1999, p. 108, which is incorporated herein by reference, describes a technique of transcranial magnetic stimulation (TMS). Using a pair of opposing pulsed magnetic fields, produced by a figure-eight coil, local eddy currents are induced in the brain near a target location. The technique has been shown to achieve stimulation of neurons at the target location by a vectorial electrical current to a resolution of 5 mm.

In an article entitled, "A technique for anodally blocking large nerve fibres through chronically implanted electrodes," by Brindley and Craggs, in *Journal of Neurology, Neurosurgery, and Psychiatry*, 1980, **43**, pp. 1083 - 1090, which is incorporated herein by reference, a method for applying electrical signals between a cathode and an anode on a spinal root of a primate is described. According to the authors, "...electrical pulses sent through these electrodes can stimulate nerve fibres close to the cathode and block the

resulting impulses close to the anode. We show (1) how anodal break excitation and excitation of fibres ... can be avoided; ... (3) that in a root containing somatic motor fibres and parasympathetic fibres, all somatic motor fibres can be blocked and most or all parasympathetic fibres excited but not blocked; ... (5) how block can be achieved in one direction only along a root; [and] (6) that a peripheral nerve can be blocked by the same techniques."

An article entitled, "Prevention of action potentials during extracellular electrical stimulation of long duration," by Zhou et al., *Journal of Cardiovascular Electrophysiology*, July, 1997, **8**, pp. 779-789, which is incorporated herein by reference, describes the application of hyperpolarizing and depolarizing shocks to papillary muscle of guinea pigs in order to prevent action potentials.

In an article by Burke and Ginsborg, entitled "The electrical properties of the slow muscle fibre membrane," *Journal of Physiology (London)*, 1956, **132**, pp. 586-598, which is incorporated herein by reference, a method is described for avoiding anode break excitation (induction of action potentials after anodal block), by making anodal block pulses cease gradually instead of suddenly. They describe removing the anodal block by exponentially decaying the original anodal block current, and setting a time constant of the exponential decay to about 30 ms.

An article by Accornero et al., entitled "Selective activation of peripheral nerve fibre groups of different diameter by triangular shaped stimulus pulses," *Journal of Physiological (London)*, 1977, **273**, pp. 539-560, which is incorporated herein by reference, describes a method for avoiding anode break excitation by applying anodal block pulses which are exponentially decayed upon removal with a range of time constants. Accornero refers to the rapid onset and the exponential decay of the anodal block pulses as having a "triangular" shape.

An article entitled, "Surface anodal stimulation of human peripheral nerves," by Winkler and Stalberg, *Experimental Brain Research*, 1988, **73**, pp. 481-488, which is incorporated herein by reference, describes the use of bipolar stimulation of nerves with short square pulses so as to elicit action potentials.

In an article by Petrofsky entitled, "Microprocessor controlled stimulation in paralyzed muscle," *IEEE NAECON Record*, December, 1979, pp. 198-210, which is incorporated herein by reference, a method is described for applying anodal block to a muscle and for sensing muscle fatigue.

US Patent 5,755,750 to Petruska et al., which is incorporated herein by reference, describes a method for selectively inhibiting activity in a nerve by applying direct current between an anode and a cathode attached to the nerve.

US Patent 5,792,186 to Rise, which is incorporated herein by reference, describes a technique for stimulating the brain to reduce the effects of neurodegenerative disorders.

US Patent 5,978,702 to Ward et al., which is incorporated herein by reference, describes techniques using one or more drugs and electrical stimulation, in order to treating a neurological disorder such as epilepsy.

US Patent 5,312,321, to Holcomb, which is incorporated herein by reference, describes a method for suppressing nerve cell action potentials using an octapolar magnetic device which generates a magnetic field near a mammalian sensory neuron.

US Patents 4,784,142 to Liss et al., 5,018,525 to Konobevtsev et al., and 5,324,317 to Reiss, which are incorporated herein by reference, describe methods for electrically stimulating a first set of nerves in order to mask the action of a second set of nerves, so as to reduce a sensation of pain.

US Patent 5,203,326 to Collins, which is incorporated herein by reference, describes an antiarrhythmic pacemaker, which stimulates the heart and also stimulates nerves or ganglia in the autonomic nervous system in order to treat the arrhythmia.

PCT Patent Publication WO 97/25098, and its corresponding national phase application US 09/101,723, entitled, "Electrical muscle controller," which are assigned to the assignee of the present patent application and are incorporated herein by reference, describe methods for modifying the force of contraction of at least a portion of a heart chamber by applying a non-excitatory electrical signal to the heart at a delay after electrical activation of the portion. The signal may be applied in combination with a pacemaker or defibrillator, which also applies an excitatory signal (i.e., pacing or defibrillation pulses) to the heart muscle. This signal can reduce or eliminate action potentials in cardiac tissue.

PCT Patent Publication WO 98/10832, and its corresponding national phase application US 09/254,900, entitled, "Cardiac output enhanced pacemaker," which are assigned to the assignee of the present patent application and are incorporated herein by reference, describe a pacemaker that modifies cardiac output. This pacemaker applies both excitatory (pacing) and non-excitatory electrical signals to the heart. By applying non-excitatory signals of suitable strength, appropriately timed with respect to the heart's electrical activation, the contraction of selected segments of the heart muscle can be increased or decreased.

## SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide apparatus and methods for controlling the electrical behavior of nervous tissue.

It is a further object of some aspects of the present invention to provide apparatus and methods for inhibiting the propagation of action potentials in nervous tissue.

It is still a further object of some aspects of the present invention to provide apparatus and methods for modulating the output frequency of a nerve cell.

It is yet a further object of some aspects of the present invention to provide improved apparatus and methods for treatment of epilepsy and other neurological disorders.

In preferred embodiments of the present invention, the electrical behavior of nervous tissue in a human subject is modified by the application of electrical energy to the tissue. An electrical transducer is placed in a vicinity of the nervous tissue. A control unit drives the transducer to apply the energy to the tissue in order to inhibit propagation therein of an action potential. The control unit preferably configures the shape of the waveform so as to reduce (a) the likelihood of the generation of an action potential when the electrical energy is removed, and/or (b) the amount of energy applied to the tissue during a designated time period.

Preferably, the transducer comprises one or more inhibiting electrodes, but the principles of the present invention may be applied using transducers of other types, such as remote electromagnetic transducers, as in the TMS technique described in the Background of the Invention.

Typically, the nervous tissue includes a target set of nerve cells and/or axons in which it is desired to inhibit the development and propagation of action potentials, in order to prevent or palliate the effects of a neurological disorder or to control pain, for example. Preferably, an operator of the control unit positions the inhibiting electrodes so that the electrical energy is applied to directly affect the behavior of the target set of nerve cells and/or axons, not necessarily having any effect on other nerve cells and/or axons not in the target set. By virtue of focusing the energy directly on the tissue of interest, this approach is different from, and. it is believed, superior to, methods known in the art such as those described in some of the above-cited patents, in which a first set of nerves is stimulated in order to mask the signals of a second set of nerves. Typically, although not necessarily, application of the electrical energy as provided by embodiments of the present invention has an inhibiting effect on the target set of nerve cells and/or axons and does not cause the generation of action potentials in nervous tissue in a vicinity thereof. In the context of the present patent application and in the claims, the term "nervous tissue" will be understood generally to apply to substantially any type of excitable tissue, as appropriate, including neurons and axons, unless there is an indication to the contrary.

Preferably, the inhibiting electrodes are applied to the tissue, and the applied electrical energy is configured so as to produce a state of "anodic block," as is well known in the art. Apparatus and techniques described in the above-cited articles and patents which relate to the induction of anodic block (in particular, the article by Brindley and Craggs), may be adapted for use on human nervous tissue as described herein, *mutatis mutandis*. However, these embodiments of the present invention preferably configure the shape of the applied electrical energy so as to achieve a greater reduction of the likelihood of generation of action potentials than is obtained using the methods described in these articles and patents. Alternatively or additionally, the applied waveform is configured so as to reduce the amount of applied energy, while yielding the same or a greater level of action potential inhibition. Typically, but not necessarily, the enhanced performance achieved using these embodiments of the present invention is obtained by providing (a) an inhibition period, in which a cathode and an anode are driven to inject current into the tissue at a generally-constant rate, and (b) a signal-removal period, following the inhibition period, during which the rate of current injection is reduced, first slowly, and then more

rapidly, until a smaller amount of current of substantially no more current is injected into the nerve. Prior art signal-removal periods, by contrast, use either a constant rate for reducing the applied current, or a rate which begins quickly and is then reduced as the current approaches zero (i.e., an exponential decrease).

As appropriate, the electrical energy applied by the inhibiting electrodes may include, alternatively or additionally, a series of pulses, each pulse preferably having a direct current (DC) component. Further alternatively or additionally, the electrical energy applied through the inhibiting electrodes includes a varying component. Typically, during an initial calibration period, different parameters of the electrical energy are varied according to an optimization procedure, to produce a desired inhibition of electrical activity in the target nervous tissue.

Preferably, an electrical sensor comprising a set of one or more sensing electrodes is also placed in a vicinity of the nervous tissue, to detect electrical activity of the tissue, and to transmit a signal responsive thereto to the control unit. The control unit typically modifies a timing parameter or other parameter of the energy application responsive to the signal. For some applications, e.g., pain reduction, the control unit evaluates the signal from the electrical sensor in order to determine when action potentials corresponding to pain signals are being transmitted in the nervous tissue, and, responsive to such a determination, drives the inhibiting electrodes to apply energy to the tissue which substantially or completely inhibits these action potentials. It is noted that applying the energy responsive to sensing, as described herein, is advantageous both because it reduces the energy expended during use of the apparatus (which is typically, but not necessarily, powered by batteries), and because it is believed to be beneficial to the stimulated nervous tissue to generally reduce the amount of energy applied thereto, where possible.

Optionally, the control unit controls the level of action potential inhibition so as to allow the human subject to sense a "useful" level of discomfort, instead of the pain which would be experienced without any action potential inhibition. Depending on the particular clinical indication, the energy may be applied to reduce or eliminate acute pain, such as during a defibrillation or a surgical procedure, or to reduce or eliminate chronic pain, such as low back pain, wrist pain, or phantom limb pain. In a preferred embodiment, use of

pain-reducing aspects of the present invention during a medical procedure permits a desired reduction in the quantity of anesthesia delivered to the subject.

Alternatively or additionally, a pacing electrode is placed in a vicinity of the nervous tissue and conveys a pacing signal generated by the control unit to the nervous tissue. The term "pacing" as used in the context of the present patent application and in the claims refers to signal pulses that repeat over time at a generally constant repetition rate. and does not specifically refer to pacing of the heart.

For some applications, a series of action potentials which repeat at a first rate are detected by the electrical sensor and are inhibited by energy from the inhibiting electrodes, and pacing pulses at a second rate are applied to the nervous tissue. When the second rate is slower than the first rate, this technique can be advantageously applied to subjects with disorders such as cerebral palsy or Parkinson's disease, so as to control muscle tremors.

In some of these preferred embodiments, the desired inhibition of the electrical activity produces a reduction in the contraction force or rate of a skeletal or smooth muscle. In one such embodiment, the inhibition is used to modulate muscle tone so as to treat degenerative diseases, such as cerebral palsy and Parkinson's disease, which are characterized by abnormal muscle contraction.

Alternatively or additionally, the excessive neuronal discharge associated with epilepsy is controlled by applying the electrical energy at or near a focus of the pathological electrical activity in the brain.

In some preferred embodiments of the present invention, a modulating electrode driven by the control unit applies an electrical modulation signal to one or more nerve cells. so as to modulate an output frequency thereof. The modulation signal is typically applied separately from the electrical energy that inhibits action potentials as described hereinabove. Preferred applications of these embodiments include reducing the subject's breathing rate or heart rate. Typically, the modulation signal comprises a pacing signal, which changes the output frequency of the paced nerve cells. Alternatively or additionally, the modulation signal comprises a blocking component, which inhibits stimulation of the nerve cell by an action potential or other electrophysiological signal. In one such preferred

embodiment, the modulation signal is used to modulate muscle tone, for treating disorders such as cerebral palsy.

There is therefore provided, in accordance with a preferred embodiment of the present invention, apparatus for modifying the electrical behavior of nervous tissue in a human subject, including:

an electrical energy sensing transducer, adapted to be placed in a first vicinity of the nervous tissue and to generate a signal responsive to electrical activity of the tissue;

an electrical energy application transducer, adapted to be placed in a second vicinity of the nervous tissue; and

a control unit, adapted to receive the signal and, responsive thereto, to drive the application transducer to apply electrical energy to the nervous tissue to inhibit propagation therein of action potentials.

Preferably, the control unit is adapted to configure a characteristic of the application of the energy so as to substantially not cause generation of an action potential in at least a portion of the nervous tissue.

In a preferred embodiment, the control unit is adapted to drive the application transducer to apply direct current and/or alternating current.

For some applications, the control unit is adapted to drive the application transducer to apply the electrical energy, so as to inhibit contraction of a skeletal and/or smooth muscle of the subject.

Preferably, the electrical energy application transducer includes one or more electrodes, which are adapted to be applied to the body of the subject. Further preferably, the electrical energy sensing transducer includes one or more electrodes, which are adapted to be applied to the body of the subject.

For some applications, the electrical energy application transducer includes a cathode and an anode, adapted to be placed at respective locations on the nervous tissue, and wherein the control unit is adapted to drive an electrical current between the cathode and the anode so as to induce anodal block in the tissue. Preferably, the control unit is adapted to reduce a level of the current at a first rate during a first current-reduction period, and, during a second current-reduction period, to reduce the level of the current at

a second rate, which is faster than the first rate. Further preferably, the control unit is adapted to reduce the level of the current at a series of three or more rates, substantially each of the rates having an equal or greater magnitude than a previous one of the rates.

In a preferred embodiment, the control unit is adapted to drive the application transducer to apply the electrical energy to the nervous tissue responsive to a level of the electrical activity. For example, the control unit may be adapted to drive the application transducer to apply the electrical energy to the nervous tissue responsive to a rate of action potential propagation in the tissue.

For some applications, the nervous tissue includes sympathetic nervous tissue, and the control unit is adapted to drive the application transducer to apply the electrical energy to the sympathetic nervous tissue so as to engender a parasympathetic response. Alternatively, the nervous tissue includes parasympathetic nervous tissue, and the control unit is adapted to drive the application transducer to apply the electrical energy to the parasympathetic nervous tissue so as to engender a sympathetic response.

In a preferred embodiment, the control unit is adapted to modify a parameter of the application of the energy responsive to the signal generated by the sensing transducer. For example, the control unit may be adapted to modify a timing parameter of the application of the energy responsive to the signal generated by the sensing transducer.

In a preferred embodiment, the nervous tissue includes a nerve, and the sensing transducer includes a proximal and a distal sensing transducer, adapted to be placed at respective proximal and distal sites with respect to a location in the nerve from which a sensory nervous signal is intermittently propagated. Preferably, the control unit is adapted to receive respective proximal signals and distal signals from the proximal and distal sensing transducers, and to drive the application transducer to apply the electrical energy responsive to the proximal and distal signals. Further preferably, the proximal and distal sensing transducers are adapted to be placed at respective proximal and distal sites with respect to a location in the nerve from which an undesired pain signal is intermittently propagated, and the control unit is adapted to receive respective proximal pain-indication signals and distal pain-indication signals from the proximal and distal sensing transducers. Still further preferably, the control unit is adapted to drive the application transducer to

apply the electrical energy responsive to the proximal and distal pain-indication signals. Typically, but not necessarily, the control unit is adapted to substantially withhold driving the application transducer to apply the electrical energy when the distal sensing transducer generates the distal pain-indication signals.

In a preferred embodiment, the sensing transducer includes a plurality of sensing electrodes, which are adapted to sense the action potentials in the tissue before the control unit drives the application transducer to apply the electrical energy to inhibit the action potentials. Preferably, the apparatus includes at least one pacing electrode, and the control unit is adapted to drive the pacing electrode to pace the tissue after one of the action potentials is sensed.

For some applications, the control unit is adapted to drive the application transducer to apply the electrical energy so as to reduce a sensation perceived by the subject. For example, the control unit may be adapted to drive the application transducer to apply the electrical energy so as to reduce a pain sensation perceived by the subject, such as a chronic pain sensation, an acute pain sensation a pain sensation perceived by the subject due to a defibrillation procedure, or a pain sensation perceived by the subject due to a surgical procedure. In this latter case, the control unit is typically, but not necessarily, adapted to drive the application transducer to apply the electrical energy so as to allow a reduction of a quantity of anesthesia normally associated with the surgical procedure.

In a preferred embodiment, the apparatus includes at least one pacing electrode, adapted to be placed in a third vicinity of the nervous tissue. The control unit is preferably adapted to drive the at least one pacing electrode to apply a pacing signal to the nervous tissue. For example, the control unit may be adapted (a) to determine responsive to the signal whether a first rate of electrical activity of the nervous tissue is above a threshold rate, (b) to drive the application transducer to apply the electrical energy responsive to determining that the activity is above the threshold rate, so as to inhibit the propagation therein of the action potentials, and (c) to drive the at least one pacing electrode to apply the pacing signal so as to engender a second rate of electrical activity of the nervous tissue which is below the threshold rate.

Typically, the control unit is adapted to determine the first level of electrical activity responsive to a rate of action potential propagation in the nervous tissue. Alternatively or additionally, the control unit is adapted to drive the at least one pacing electrode to apply the pacing signal so as to increase a level of muscle tone of a muscle whose behavior is modulated by the nervous tissue. Further alternatively or additionally, the control unit is adapted to drive the at least one pacing electrode to apply the pacing signal so as to improve functioning of a muscle.

There is further provided, in accordance with a preferred embodiment of the present invention, apparatus for controlling epilepsy in a human subject, including:

at least one electrical energy transducer, adapted to be coupled to a brain of the subject; and

a control unit, which drives the at least one transducer to apply electrical energy to a portion of the brain to inhibit propagation therein of an action potential related to the epilepsy, so as to control the epilepsy.

Preferably, the at least one electrical energy transducer includes a cathode and an anode, and the control unit is adapted to drive an electrical current between the cathode and the anode so as to induce anodal block in the portion of the brain.

Further preferably, the control unit is adapted to configure the application of the electrical energy so as to substantially not cause generation of an action potential in at least a sub-portion of the portion of the brain.

In a preferred embodiment, the apparatus includes at least one electrical sensor, adapted to be placed in a vicinity of the portion of the brain to sense electrical activity of the portion of the brain, and adapted to convey a signal to the control unit responsive to the sensing. Preferably, the control unit is adapted to set a parameter of the application of the energy applied by the electrical energy transducer responsive to the signal.

Alternatively or additionally, the apparatus includes at least one pacing transducer, adapted to be placed in a vicinity of the portion of the brain, and the control unit is adapted to drive the at least one pacing transducer to apply a pacing signal to the portion of the brain.

There is still further provided, in accordance with a preferred embodiment of the present invention, apparatus for modulating an output of a nerve cell in a human subject, including:

a modulating transducer, adapted to be electrically coupled to the nerve cell; and

a control unit, adapted to drive the modulating transducer to apply electrical energy to the nerve cell so as to modulate an output frequency thereof.

In a preferred embodiment, the control unit is adapted to drive the transducer to apply a pacing signal to the nerve cell.

Alternatively or additionally, the control unit is adapted to configure the electrical energy to include a blocking component, which inhibits an action potential from stimulating the nerve cell.

For some applications, the control unit is adapted to drive the transducer to apply the electrical energy so as to modify a breathing rate and/or a heart rate of the subject.

Typically, but not necessarily, the control unit is adapted to configure the electrical energy so as to substantially not cause generation of an action potential in a vicinity of the nerve cell.

Preferably, the modulating transducer includes an electrode, which is adapted to be applied to the body of the subject. In addition, the apparatus preferably includes at least one electrical sensor, coupled to the control unit, which is adapted to be placed in a vicinity of the nerve cell and to sense electrical activity of the nerve cell. The control unit is preferably adapted to set a parameter of the application of the energy responsive to the sensed electrical activity.

There is yet further provided, in accordance with a preferred embodiment of the present invention, apparatus for modulating a characteristic of muscle tissue of a human subject, including:

a pacing transducer, adapted to be applied in a first vicinity of nervous tissue that modulates behavior of the muscle tissue;

an inhibiting transducer, adapted to be applied in a second vicinity of the nervous tissue; and

a control unit, adapted to drive the inhibiting transducer to apply an inhibiting signal to the nervous tissue so as to inhibit propagation of an action potential in the tissue, and adapted to drive the pacing transducer to apply a pacing signal, so as to induce propagation of an action potential in the tissue, so as to modulate the characteristic of the muscle tissue.

Preferably, the inhibiting transducer includes a cathode and an anode, and the control unit is adapted to drive an electrical current between the cathode and the anode so as to induce anodal block in the nervous tissue. In a preferred embodiment, the control unit is adapted to drive the transducers to apply the signals so as to modify tone of the muscle tissue. Alternatively or additionally, the control unit is adapted to drive the transducers to apply the signals so as to modify contraction strength of the muscle tissue. Still further alternatively or additionally, the control unit is adapted to drive the transducers to apply the signals so as to treat a dysfunction of the muscle tissue.

In a preferred embodiment, the apparatus includes a sensing transducer, adapted to sense a first plurality of action potentials having a first rate, and the control unit is adapted to drive the inhibiting transducer to apply the inhibiting signal so as to inhibit the first plurality of action potentials. In addition, the control unit is preferably adapted to drive the pacing transducer to apply the pacing signal so as to induce propagation of a second plurality of action potentials having a second rate. As appropriate, the control unit may be adapted to set the second rate to be lower than the first rate or higher than the first rate.

There is also provided, in accordance with a preferred embodiment of the present invention, a method for modifying the electrical behavior of nervous tissue in a human subject, including:

sensing electrical activity of the nervous tissue; and

applying electrical energy to the nervous tissue, responsive to the sensing, so as to inhibit propagation in the tissue of an action potential.

Typically, but not necessarily, applying the electrical energy includes injecting current into the tissue so as to induce anodal block in the tissue.

In a preferred embodiment, applying the electrical energy includes applying the energy so as to modify a sensation perceived by the subject.

Preferably, the method includes sensing an action potential in the tissue and pacing the tissue responsive to the sensing. Further preferably, applying electrical energy to the nervous tissue includes applying energy to inhibit propagation of an action potential after the tissue is paced.

In a preferred embodiment, the method includes sensing further electrical activity of the tissue after applying the energy to inhibit the propagation, in order to verify that inhibition has taken place.

There is additionally provided, in accordance with a preferred embodiment of the present invention, a method for modulating a characteristic of muscle tissue of a human subject, including:

applying inhibitory electrical energy to nervous tissue of the subject, so as to inhibit propagation of an action potential in the nervous tissue; and

applying a pacing signal to the nervous tissue, so as to modulate the characteristic of the muscle tissue.

There is still additionally provided, in accordance with a preferred embodiment of the present invention, a method for controlling epilepsy in a human subject, including applying electrical energy to a portion of a brain of the subject to inhibit propagation therein of an action potential related to the epilepsy, so as to control the epilepsy.

There is yet additionally provided, in accordance with a preferred embodiment of the present invention, a method for modulating an output of a nerve cell in a human subject, including applying electrical energy to the nerve cell so as to modulate an output frequency thereof. Optionally, applying the electrical energy includes applying electrical energy including a blocking component, so as to inhibit an action potential from stimulating the nerve cell.

The present invention will be more fully understood from the following detailed description of the preferred embodiments thereof, taken together with the drawings, in which:

## BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a simplified pictorial illustration showing apparatus for control of electrophysiological activity, in accordance with a preferred embodiment of the present invention;

Fig. 2 is a schematic block diagram showing components of the apparatus of Fig. 1, in accordance with a preferred embodiment of the present invention;

Fig. 3 is a simplified pictorial illustration showing the apparatus of Fig. 1 configured for use in a typical application, in accordance with a preferred embodiment of the present invention; and

Fig. 4 is a graph showing a signal application protocol for application by the apparatus shown in Fig. 1, in accordance with a preferred embodiment of the present invention.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Fig. 1 is a simplified pictorial illustration showing apparatus 20 for control of electrophysiological activity of nervous tissue 30 of a human subject, in accordance with a preferred embodiment of the present invention. Apparatus 20 comprises a control unit 40, coupled to control one or more inhibiting electrodes 22 placed in a vicinity of the nervous tissue. The inhibiting electrodes apply electrical energy to the tissue in order to inhibit development and/or propagation therein of an action potential. In some embodiments, the applied electrical energy has characteristics, including amplitude, frequency, and shape, similar to corresponding characteristics of non-excitatory signals described in the above-cited PCT patent publications and their corresponding US patent applications. Alternatively or additionally, some embodiments of the present invention utilize methods and apparatus described in US Patent Application 09/368,124, entitled, "Inhibition of action potentials," which is assigned to the assignee of the present patent application and is incorporated herein by reference.

Preferably, one or more local sense electrodes 24 are placed on or near the nervous tissue. Electrodes 24 typically comprise paired differential electrodes 24A and 24B, as shown in the figure. The local sense electrodes are preferably coupled to detect electrical activity of the tissue and convey a signal responsive thereto to control unit 40, which may subsequently modify the energy conveyed through inhibiting electrodes 22. For some

applications, one or more pacing electrodes 26 are placed in a vicinity of the nervous tissue to convey a pacing signal to the nervous tissue, as described hereinbelow.

In the preferred embodiment shown in Fig. 1, local sense electrodes 24 are placed both "upstream" and "downstream" of inhibiting electrodes 22 (with respect to the direction of propagation of action potentials in tissue 30). In this manner, the upstream sense electrodes can provide an indication of action potentials propagating in the tissue, responsive to which apparatus 20 applies energy to electrodes 22 and/or 26. Preferably, the downstream sense electrodes provide feedback as to the effectiveness of the applied energy in inhibiting the action potentials.

In a preferred application, a series of action potentials which repeat at a first rate are detected by sensing electrodes 24A, and are inhibited by energy applied by inhibiting electrodes 22. Optionally, control unit 40 drives pacing electrodes 26 to apply pacing pulses at a second rate which is lower than the first rate. This technique is advantageously applied, for example, in tissue which innervates a muscle that frequently demonstrates tremors, such as in subjects with cerebral palsy or Parkinson's disease.

Although preferred embodiments are described herein with reference to electrodes 22, 24 and 26, it will be understood that transducers of other types, as are known in the art, may also be used to apply electrical energy to tissue 30 and/or to sense electrical activity in the tissue. For example, electromagnetic transducers such as those described in the above-cited article entitled "Biomagnetic approaches to studying the brain" may also be used for this purpose. It is further to be understood that for clarity, various types of electrodes shown in the figures are described as performing distinct functions. However, for some applications, some or all of the electrodes perform a plurality of functions, e.g., inhibiting, sensing, and pacing.

Fig. 2 is a schematic block diagram of control unit 40, in accordance with a preferred embodiment of the present invention. A parameter determination block 42 of the control unit, typically comprising a CPU and an electronic memory (not shown), preferably sets parameters of the electrical energy delivered through one or more signal application electrodes 50 placed in a vicinity of nervous tissue 30. Further preferably, block 42 sets parameters of the pacing signal applied to the tissue through pacing

electrodes 26. Although signal application electrodes 50 typically comprise inhibiting electrodes 22 (described with reference to Fig. 1), in some embodiments, electrodes 50 alternatively or additionally comprise modulating electrodes, described hereinbelow, which modulate an output frequency of one or more nerve cells.

The parameters set by block 42 typically include magnitude, frequency, DC offset, pulse decay features, and a base wave shape, such as DC, sinusoidal, square, or shaped pulses. Additionally, block 42 preferably selects either a current-delivery mode or a voltage-application mode of energy transfer into nervous tissue 30. A particular preferred signal application protocol is described hereinbelow with reference to Fig. 4.

In regular use, parameter determination block 42 typically receives signals from local sense electrodes 24, responsive to electrical activity of nervous tissue 30. Responsive to the signals, block 42 modifies a timing or other parameter of the electrical energy delivered through electrodes 50, and/or of the pacing signal delivered through electrodes 26. Preferably, an appropriate parameter modification strategy is generated during an initial calibration period of the control unit, described hereinbelow. Alternatively or additionally, a human operator of control unit 40 may utilize operator controls 32 (e.g., a keyboard) to participate in, or override, the determination of parameters by block 42. Further alternatively or additionally, subject controls 34, typically comprising a keypad, wheel, on/off switch, timer, or slide-bar (not shown), permit the subject to give feedback to the control unit, in order to optimize the parameter determination. The subject controls are used to particular advantage in pain-reduction applications of the present invention, as described hereinbelow.

Preferably, the parameters determined by block 42 are conveyed to a signal generation block 44 of control unit 40, which generates, responsive to the parameters, electrical signals that are applied by signal application electrodes 50 and pacing electrodes 26 to nervous tissue 30. Block 44 preferably comprises amplifiers, isolation units, and other standard circuitry known in the art of electrical signal generation for application of signals to the body.

In a preferred embodiment, the desired inhibition of the electrical activity of nervous tissue 30 produces a reduction in the contraction force of a skeletal or smooth

muscle innervated by tissue 30. This may be used, for example, to transiently induce local paralysis during surgery, to control a chronically-recurring spasm or tremor, or to treat muscle-tension headache.

In another preferred embodiment, the excessive neuronal discharge associated with epilepsy is controlled by applying the electrical energy at or near a focus of the pathological electrical activity. Typically, during an initial therapeutic session, a physician determines appropriate locations for placement of electrodes 50, 26, and 24, which are subsequently permanently implanted. Preferably, control unit 40 is portable or implantable, and periodically transmits stored data to an evaluation unit (not shown), to allow the physician to evaluate the success of a particular epilepsy control strategy, and to reprogram parameter determination block 42 if necessary. Optionally, some methods and apparatus described in the above-cited US Patent 5,792,186 to Rise are utilized in practicing this embodiment of the present invention.

For some applications, control unit 40 drives signal application electrodes 50 to apply an inhibition signal so as to reduce a sensation (for example, pain), by eliminating the action potentials or by reducing the rate and/or duration of a series of action potentials which convey the pain sensation. Preferably, the control unit initiates the inhibition signal responsive to signals from local sense electrodes 24 indicative of the onset of a pain sensation (for example, using techniques known in the art and/or as described hereinbelow with reference to Fig. 3). Alternatively or additionally, the inhibition signal is applied responsive to an input through subject controls 34 indicating that the subject is experiencing pain. Depending on the particular application, the energy may be applied to reduce or eliminate acute pain, such as during a defibrillation or a surgical procedure, or to reduce or eliminate chronic pain, such as low back pain, wrist pain, or phantom limb pain. In a preferred embodiment, use of pain-reducing aspects of the present invention during a medical procedure permits a desired reduction in the quantity of anesthesia delivered to the subject.

Typically, during the initial calibration period, different parameters of the applied electrical energy and/or pacing signal are varied according to an optimization procedure, to produce a desired inhibition of electrical activity in nervous tissue 30. Preferably, parameter determination block 42 modifies a characteristic (e.g., timing, magnitude, or

shape) of signals applied through electrodes 50 or 26, and then determines whether a measured response generally improves following the modification. The response may be, for example, an aspect of a force generated in a muscle, a signal from local sense electrodes 24, a characteristic of an electroencephalogram, or an indication of pain perceived by the subject, which is input through subject controls 34. In a series of similar calibration steps, block 42 preferably iteratively modifies characteristics of the signals applied through the electrodes, such that those modifications that improve the response are generally maintained, and modifications that cause it to worsen are typically eliminated or avoided.

For some applications, signal application electrodes 50 comprise one or more modulating electrodes, which apply an electrical modulation signal to nervous tissue 30, so as to modulate an output frequency of one or more nerve cells therein. The modulation signal is typically, but not necessarily, applied at a separate time from, or to the exclusion of, the electrical energy which inhibits action potentials described hereinabove. Preferred applications of this embodiment include, for example, increasing or decreasing the subject's breathing rate or heart rate. Typically, the modulation signal comprises a pacing signal, as described hereinabove, which changes the output frequency of the paced nerve cell(s). Alternatively or additionally, the modulation signal comprises a blocking component, which inhibits stimulation of nerve cells in tissue 30 by some or all nerve cells connected thereto. It is noted that vagus nerve stimulation techniques known in the art *stimulate* the vagus nerve in order to increase its firing rate and to thereby decrease the heart rate, unlike embodiments of the present invention wherein electrical energy is applied to nervous tissue to control action potential generation and/or propagation by means of inhibition and, optionally, pacing. In particular, embodiments of the present invention described in this application enable the application of inhibiting energy to sympathetic nerves, in order to obtain a parasympathetic response (e.g., to reduce respiration rate or heart rate), or, by contrast, the application of inhibiting energy to parasympathetic nerves so as to obtain a sympathetic response (e.g., to increase respiration rate or heart rate).

Fig. 3 is a simplified pictorial illustration showing apparatus 20 in one preferred configuration thereof, in accordance with a preferred embodiment of the present invention.

As shown in the figure, a plurality of electrodes 100, including some or all of the electrodes shown in Fig. 1, are implanted within the body of the subject in a vicinity of, or preferably in contact with, a nerve 70, such as an intercostal nerve. Preferably, but not necessarily, at least some of electrodes 100 are positioned near the spinal column. Control unit 40 is preferably implanted in the subject's body, either in proximity to nerve 70, or at another location within the subject's body, as appropriate. Control unit 40 and electrodes 100 are typically implanted using techniques known in the art for chronic implantation of bioelectrical apparatus. Suitable methods are described, for example, in the above-referenced article by Brindley and Craggs. It will be appreciated that techniques which are useful in the construction and implantation of pacemakers are similarly useful in applying some of the principles of the present invention, *mutatis mutandis*. It is also to be understood that, although Fig. 3 shows control unit 40 and all of electrodes 100 as being implanted in the subject, for some other applications of the invention, the control unit and/or some or all of electrodes 100 may be completely external to the subject. Moreover, for some applications, some or all of the electrodes are passed through the skin of the subject, so as to be positioned in a vicinity of nerve 70.

Electrodes 100 and control unit 40 are typically not implanted when apparatus 20 is designated for usage during a relatively-limited period, such as for pain-relief applications during the first day or several days following a traumatic injury to the chest which, for example, breaks one or more ribs. Implanting the control unit and electrodes, by contrast, is often appropriate during intensive thoracic surgery in which a rib retractor is used, that, without treatment, may cause prolonged intense pain in some patients. Preferably, the implanted apparatus is implanted using techniques which allow for relatively easy removal thereof. For implanted electrodes as well as for non-implanted electrodes, it is advantageous to use these embodiments of the present invention both so as to relieve the subject's pain, and because it is known in the art that patients who experience distress when breathing may adversely modify their respiration pattern, leading to pulmonary collapse. Although thoracic pain relief is a preferred embodiment of the present invention, it is nevertheless to be understood that the principles of the present invention could be applied for non-thoracic pain relief applications, as well as for inhibiting action potentials unrelated to pain signals.

Preferably, electrodes 100 comprise a plurality of local sense electrodes 24, which are positioned at various locations along the length of nerve 70. Control unit 40 is preferably programmed to determine that pain signals are being transmitted through the nerve if the plurality of local sense electrodes detect a wave of action potential propagation moving towards the brain, having a conduction velocity or other aspect which is characteristic of a pain signal. Typically, such a conduction velocity is determined during an initial calibration period of apparatus 20. Alternatively or additionally, the subject is instructed to press a button on subject controls 34 every time pain is present, and algorithms running in control unit 40 (e.g., artificial neural network algorithms) determine characteristics of the signals detected by local sense electrodes 24 that frequently correspond in time to the subject's indications of sensed pain. Responsive to determining that the subject is experiencing pain, control unit 40 drives one or more of electrodes 100 to apply an inhibition signal, so as to transiently reduce or eliminate the propagation of action potentials associated with the pain signal.

For some applications, it is desirable to place electrodes 100 on nerve 70, close to the subject's spinal column (as shown in Fig. 3), so as to suppress pain sensations initiated anywhere in the zone innervated by the nerve. Alternatively, proximal and distal electrodes drawn from electrodes 100 are positioned on nerve 70 near an entry location on the nerve, where pain sensations from a surgical site enter the nerve to be conveyed to the spinal cord and to the brain. In this case, the proximal electrodes are preferably placed on nerve 70 nearer to the spinal column than the entry site, and the distal electrodes are placed on the nerve at a site distal to the entry location. Pain signals which are detected by the proximal electrodes but not by the distal electrodes are preferably suppressed using the techniques described herein, if the subject's physician believes that these pain signals are a result of the surgery and are thus likely to be causing pain without serving a useful purpose. However, pain signals which are detected by both the proximal and the distal electrodes are preferably not suppressed, because they are likely not to be a result of the surgery, and are therefore probably conveying a useful pain signal (e.g., the subject is touching something hot).

Fig. 4 is a graph (not to scale) showing an inhibition signal application protocol for use by apparatus 20, in accordance with a preferred embodiment of the present invention.

Typically, but not necessarily, local sense electrodes 24 sense the initiation of a pain signal or other bioelectrical signal at a time $t_{sense}$. At a time $t_{on}$ following $t_{sense}$, control unit 40 drives one or more of electrodes 22 to inject a direct current of magnitude $I_{on}$ into nervous tissue 30. At a time $t_{reduce}$ subsequent to $t_{on}$, the control unit causes electrodes 22 to reduce the magnitude of the applied direct current from $I_{on}$ to zero. As shown in the figure, this reduction is initially implemented at a slow rate, and gradually increases to a faster rate until a time $t_{off}$, when the magnitude of the applied current reaches zero. By contrast, it is noted that prior art anodal block techniques, such as those described in the Background section of the present patent application, typically cause an exponential or linear decay of the applied current.

Preferably, electrodes 22 are positioned using techniques known in the art, such that the application of the current during the time period between $t_{on}$ and $t_{reduce}$ causes anodal block in nervous tissue 30, thereby inhibiting propagation of action potentials in a vicinity of one of electrodes 22 which is acting as an anode. By contrast, one of electrodes 22 which acts as a cathode typically does induce at least one action potential. This action potential propagates towards the anode, but advantageously, generally does not pass the anode because of the applied block. Thus, for applications such as pain relief or muscle control, the cathode-generated action potentials have substantially no negative effect on the subject, because the generated action potentials do not reach the subject's brain or muscles, respectively.

It is known that the initiation of anodal block hyperpolarizes nervous tissue to which the block is applied. As shown in the figure, the membrane voltage $V_m$ moves from a first membrane voltage $V_{m1}$ to a second membrane voltage $V_{m2}$ during the application of the current $I_{on}$. In addition, it is also known that the threshold voltage $V_t$ at which the nervous tissue would generate an action potential also increases in magnitude (i.e., becomes more negative) with the application of the current. It is to be understood that the response of the nervous tissue shown in the upper graph in Fig. 4 is to be interpreted as a schematic illustration, and not as a representation of measured data.

If the applied current is suddenly removed, then the hyperpolarized membrane typically returns to the original voltage $V_{m1}$ faster than the threshold voltage $V_t$ returns to its original voltage $V_{t1}$. Under some conditions, this may cause the magnitude of $V_m$ to

be smaller than the magnitude of $V_t$, thereby initiating an undesired action potential. Prior art techniques, such as those described in the articles and patents listed in the Background section of the present patent application, avoid this phenomenon of "anodal block break excitation" by prolonging the removal of the applied current, such that the magnitude of the threshold voltage $V_t$ is able to decrease in step with the decrease in magnitude of the membrane voltage $V_m$, thereby generally preventing the generation of an action potential. Typically, these prior art techniques apply an exponential decay to the applied current over a relatively long period.

By contrast, the protocol shown in Fig. 4 utilizes a "concave down" current removal strategy, which is typically of shorter duration than the current-removal periods which are possible using the prior art techniques. The relatively-steep initial decrease in current associated with prior art exponential decay protocols would cause break excitation if the time constant of the decay is too short, because a too-short time constant is essentially equivalent to suddenly removing the applied current. Therefore, the time constant in these prior art techniques is generally relatively long. During this period, more current is injected than is necessary, and therefore more energy is expended than is necessary.

Because the protocol in Fig. 4 utilizes a differently-shaped waveform which bears essentially no resemblance to a sudden removal of current, the inventors believe that it is possible to reduce the duration of the current removal period below that which is possible using the prior art techniques. Advantageously, reducing the time period also generally reduces the total amount of current which is applied during the current removal period, and, therefore, typically achieves one or more of the following:

- an extension of battery life (for those applications in which a battery is used),
- an increase of a repetition rate associated with multiple applications of anodal block, substantially without needing to continually apply current (only one application is shown in Fig. 4),
- a reduction of the adverse effects of polarization, and
- a minimization or essential elimination of any adverse effects in the tissue which might be caused by prior art techniques.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove and in the above-cited articles, patents, and patent applications, as well as variations and modifications thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description.

## CLAIMS

1. Apparatus for modifying the electrical behavior of nervous tissue in a human subject, comprising:

an electrical energy sensing transducer, adapted to be placed in a first vicinity of the nervous tissue and to generate a signal responsive to electrical activity of the tissue;

an electrical energy application transducer, adapted to be placed in a second vicinity of the nervous tissue; and

a control unit, adapted to receive the signal and, responsive thereto, to drive the application transducer to apply electrical energy to the nervous tissue to inhibit propagation therein of action potentials.

2. Apparatus according to claim 1, wherein the control unit is adapted to configure a characteristic of the application of the energy so as to substantially not cause generation of an action potential in at least a portion of the nervous tissue.

3. Apparatus according to claim 1, wherein the control unit is adapted to drive the application transducer to apply direct current.

4. Apparatus according to claim 1, wherein the control unit is adapted to drive the application transducer to apply alternating current.

5. Apparatus according to claim 1, wherein the control unit is adapted to drive the application transducer to apply the electrical energy, so as to inhibit contraction of a skeletal muscle of the subject.

6. Apparatus according to claim 1, wherein the control unit is adapted to drive the application transducer to apply the electrical energy, so as to inhibit contraction of a smooth muscle of the subject.

7. Apparatus according to claim 1, wherein the electrical energy application transducer comprises one or more electrodes, which are adapted to be applied to the body of the subject.

8. Apparatus according to claim 1, wherein the electrical energy sensing transducer comprises one or more electrodes, which are adapted to be applied to the body of the subject.

9. Apparatus according to claim 1, wherein the control unit is adapted to drive the application transducer to apply the electrical energy to the nervous tissue, the nervous tissue including sympathetic nervous tissue, so as to engender a parasympathetic response.

10. Apparatus according to claim 1, wherein the control unit is adapted to drive the application transducer to apply the electrical energy to the nervous tissue, the nervous tissue including parasympathetic nervous tissue, so as to engender a sympathetic response.

11. Apparatus according to any one of claims 1-10, wherein the electrical energy application transducer comprises a cathode and an anode, adapted to be placed at respective locations on the nervous tissue, and wherein the control unit is adapted to drive an electrical current between the cathode and the anode so as to induce anodal block in the tissue.

12. Apparatus according to claim 11, wherein the control unit is adapted to reduce a level of the current at a first rate during a first current-reduction period, and, during a second current-reduction period, to reduce the level of the current at a second rate, which is faster than the first rate.

13. Apparatus according to claim 12, wherein the control unit is adapted to reduce the level of the current at a series of three or more rates, substantially each of the rates having an equal or greater magnitude than a previous one of the rates.

14. Apparatus according to any one of claims 1-10, wherein the control unit is adapted to drive the application transducer to apply the electrical energy to the nervous tissue responsive to a level of the electrical activity.

15. Apparatus according to claim 14, wherein the control unit is adapted to drive the application transducer to apply the electrical energy to the nervous tissue responsive to a rate of action potential propagation in the tissue.

16. Apparatus according to any one of claims 1-10, wherein the control unit is adapted to modify a parameter of the application of the energy responsive to the signal generated by the sensing transducer.

17. Apparatus according to claim 16, wherein the control unit is adapted to modify a timing parameter of the application of the energy responsive to the signal generated by the sensing transducer.

18. Apparatus according to any one of claims 1-10, wherein the nervous tissue includes a nerve, wherein the sensing transducer comprises a proximal and a distal sensing transducer, adapted to be placed at respective proximal and distal sites with respect to a location in the nerve from which a sensory nervous signal is intermittently propagated, wherein the control unit is adapted to receive respective proximal signals and distal signals from the proximal and distal sensing transducers, and wherein the control unit is adapted to drive the application transducer to apply the electrical energy responsive to the proximal and distal signals.

19. Apparatus according to any one of claims 1-10, wherein the nervous tissue includes a nerve, wherein the sensing transducer comprises a proximal and a distal sensing transducer, adapted to be placed at respective proximal and distal sites with respect to a location in the nerve from which an undesired pain signal is intermittently propagated, wherein the control unit is adapted to receive respective proximal pain-indication signals and distal pain-indication signals from the proximal and distal sensing transducers, and wherein the control unit is adapted to drive the application transducer to apply the electrical energy responsive to the proximal and distal pain-indication signals.

20. Apparatus according to claim 19, wherein the control unit is adapted to substantially withhold driving the application transducer to apply the electrical energy when the distal sensing transducer generates the distal pain-indication signals.

21. Apparatus according to any one of claims 1-10, wherein the sensing transducer comprises a plurality of sensing electrodes, which are adapted to sense the action potentials in the tissue before the control unit drives the application transducer to apply the electrical energy to inhibit the action potentials.

22. Apparatus according to claim 21, and comprising at least one pacing electrode, wherein the control unit is adapted to drive the pacing electrode to pace the tissue after one of the action potentials is sensed.

23. Apparatus according to any one of claims 1-10, wherein the control unit is adapted to drive the application transducer to apply the electrical energy so as to reduce a sensation perceived by the subject.

24. Apparatus according to claim 23, wherein the control unit is adapted to drive the application transducer to apply the electrical energy so as to reduce a pain sensation perceived by the subject.

25. Apparatus according to claim 24, wherein the control unit is adapted to drive the application transducer to apply the electrical energy so as to reduce a chronic pain sensation perceived by the subject.

26. Apparatus according to claim 24, wherein the control unit is adapted to drive the application transducer to apply the electrical energy so as to reduce an acute pain sensation perceived by the subject.

27. Apparatus according to claim 24, wherein the control unit is adapted to drive the application transducer to apply the electrical energy so as to reduce a pain sensation perceived by the subject due to a defibrillation procedure.

28. Apparatus according to claim 24, wherein the control unit is adapted to drive the application transducer to apply the electrical energy so as to reduce a pain sensation perceived by the subject due to a surgical procedure.

29. Apparatus according to claim 28, wherein the control unit is adapted to drive the application transducer to apply the electrical energy so as to allow a reduction of a quantity of anesthesia normally associated with the surgical procedure.

30. Apparatus according to any one of claims 1-10, and comprising at least one pacing electrode, adapted to be placed in a third vicinity of the nervous tissue, wherein the control unit is adapted to drive the at least one pacing electrode to apply a pacing signal to the nervous tissue.

31. Apparatus according to claim 30, wherein the control unit is adapted (a) to determine responsive to the signal whether a first rate of electrical activity of the nervous tissue is above a threshold rate, (b) to drive the application transducer to apply the electrical energy responsive to determining that the activity is above the threshold rate, so

as to inhibit the propagation therein of the action potentials, and (c) to drive the at least one pacing electrode to apply the pacing signal so as to engender a second rate of electrical activity of the nervous tissue which is below the threshold rate.

32. Apparatus according to claim 31, wherein the control unit is adapted to determine the first rate of electrical activity responsive to a rate of action potential propagation in the nervous tissue.

33. Apparatus according to claim 31, wherein the control unit is adapted to drive the at least one pacing electrode to apply the pacing signal so as to increase a level of muscle tone of a muscle whose behavior is modulated by the nervous tissue.

34. Apparatus according to claim 31, wherein the control unit is adapted to drive the at least one pacing electrode to apply the pacing signal so as to improve functioning of a muscle.

35. Apparatus for controlling epilepsy in a human subject, comprising:

at least one electrical energy transducer, adapted to be coupled to a brain of the subject; and

a control unit, which drives the at least one transducer to apply electrical energy to a portion of the brain to inhibit propagation therein of an action potential related to the epilepsy, so as to control the epilepsy.

36. Apparatus according to claim 35, wherein the at least one electrical energy transducer comprises a cathode and an anode, and wherein the control unit is adapted to drive an electrical current between the cathode and the anode so as to induce anodal block in the portion of the brain.

37. Apparatus according to claim 35, wherein the control unit is adapted to configure the application of the electrical energy so as to substantially not cause generation of an action potential in at least a sub-portion of the portion of the brain.

38. Apparatus according to claim 35, and comprising at least one electrical sensor, adapted to be placed in a vicinity of the portion of the brain to sense electrical activity of the portion of the brain, and adapted to convey a signal to the control unit responsive to the sensing, wherein the control unit is adapted to set a parameter of the application of the energy applied by the electrical energy transducer responsive to the signal.

39. Apparatus according to any one of claims 35-38, and comprising at least one pacing transducer, adapted to be placed in a vicinity of the portion of the brain, wherein the control unit is adapted to drive the at least one pacing transducer to apply a pacing signal to the portion of the brain.

40. Apparatus for modulating an output of a nerve cell in a human subject, comprising:

a modulating transducer, adapted to be electrically coupled to the nerve cell; and

a control unit, adapted to drive the modulating transducer to apply electrical energy to the nerve cell so as to modulate an output frequency thereof.

41. Apparatus according to claim 40, wherein the control unit is adapted to drive the transducer to apply a pacing signal to the nerve cell.

42. Apparatus according to claim 40, wherein the control unit is adapted to configure the electrical energy to include a blocking component, which inhibits an action potential from stimulating the nerve cell.

43. Apparatus according to claim 40, wherein the control unit is adapted to drive the transducer to apply the electrical energy so as to modify a breathing rate of the subject.

44. Apparatus according to claim 40, wherein the control unit is adapted to drive the transducer to apply the electrical energy so as to modify a heart rate of the subject.

45. Apparatus according to claim 40, wherein the control unit is adapted to configure the electrical energy so as to substantially not cause generation of an action potential in a vicinity of the nerve cell.

46. Apparatus according to claim 40, wherein the modulating transducer comprises an electrode, which is adapted to be applied to the body of the subject.

47. Apparatus according to any one of claims 40-46, and comprising at least one electrical sensor, coupled to the control unit, which is adapted to be placed in a vicinity of the nerve cell and to sense electrical activity of the nerve cell, wherein the control unit is adapted to set a parameter of the application of the energy responsive to the sensed electrical activity.

48. Apparatus for modulating a characteristic of muscle tissue of a human subject, comprising:

a pacing transducer, adapted to be applied in a first vicinity of nervous tissue that modulates behavior of the muscle tissue;

an inhibiting transducer, adapted to be applied in a second vicinity of the nervous tissue; and

a control unit, adapted to drive the inhibiting transducer to apply an inhibiting signal to the nervous tissue so as to inhibit propagation of an action potential in the tissue, and adapted to drive the pacing transducer to apply a pacing signal, so as to induce propagation of an action potential in the tissue, so as to modulate the characteristic of the muscle tissue.

49. Apparatus according to claim 48, wherein the inhibiting transducer comprises a cathode and an anode, and wherein the control unit is adapted to drive an electrical current between the cathode and the anode so as to induce anodal block in the nervous tissue.

50. Apparatus according to claim 48, wherein the control unit is adapted to drive the transducers to apply the signals so as to modify tone of the muscle tissue.

51. Apparatus according to claim 48, wherein the control unit is adapted to drive the transducers to apply the signals so as to modify contraction strength of the muscle tissue.

52. Apparatus according to claim 48, wherein the control unit is adapted to drive the transducers to apply the signals so as to treat a dysfunction of the muscle tissue.

53. Apparatus according to any one of claims 48-52, and comprising a sensing transducer, adapted to sense a first plurality of action potentials having a first rate, wherein the control unit is adapted to drive the inhibiting transducer to apply the inhibiting signal so as to inhibit the first plurality of action potentials, and wherein the control unit is adapted to drive the pacing transducer to apply the pacing signal so as to induce propagation of a second plurality of action potentials having a second rate.

54. Apparatus according to claim 53, wherein the control unit is adapted to set the second rate to be lower than the first rate.

55. Apparatus according to claim 53, wherein the control unit is adapted to set the second rate to be higher than the first rate.

56. A method for modifying the electrical behavior of nervous tissue in a human subject, comprising:

sensing electrical activity of the nervous tissue; and

applying electrical energy to the nervous tissue, responsive to the sensing, so as to inhibit propagation in the tissue of an action potential.

57. A method according to claim 56, wherein applying the electrical energy comprises configuring the energy so as to substantially not cause generation of an action potential in at least a portion of the nervous tissue.

58. A method according to claim 56, wherein applying the electrical energy comprises applying direct current to the tissue.

59. A method according to claim 56, wherein applying the electrical energy comprises applying alternating current to the tissue.

60. A method according to claim 56, wherein applying the electrical energy comprises applying the electrical energy so as to inhibit contraction of a skeletal muscle of the subject.

61. A method according to claim 56, wherein applying the electrical energy comprises applying the electrical energy so as to inhibit contraction of a smooth muscle of the subject.

62. A method according to claim 56, wherein the nervous tissue includes a nerve, wherein sensing the electrical activity comprises sensing electrical activity at respective proximal and distal sites with respect to a location in the nerve from which an undesired pain signal is intermittently propagated, and wherein applying the electrical energy comprises substantially withholding the application of the energy responsive to sensing electrical activity indicative of pain at the distal site.

63. A method according to claim 56, wherein applying the electrical energy to the nervous tissue comprises applying the electrical energy to the nervous tissue, the nervous tissue including sympathetic nervous tissue, so as to engender a parasympathetic response.

64. A method according to claim 56, wherein applying the electrical energy to the nervous tissue comprises applying the electrical energy to the nervous tissue, the nervous tissue including parasympathetic nervous tissue, so as to engender a sympathetic response.

65. A method according to any one of claims 56-64, wherein applying the electrical energy comprises setting a parameter of the application of the energy responsive to the sensed electrical activity.

66. A method according to claim 65, wherein setting the parameter comprises setting a timing parameter.

67. A method according to claim 56, wherein applying the electrical energy comprises injecting current into the tissue so as to induce anodal block in the tissue.

68. A method according to claim 67, and comprising:

reducing a level of the current at a first rate during a first current-reduction period; and

during a second current-reduction period, reducing the level of the current at a second rate, which is faster than the first rate.

69. A method according to claim 67, and comprising reducing a level of the current at a series of rates, substantially each of the rates having an equal or greater magnitude than a previous one of the rates.

70. A method according to any one of claims 56-64, wherein applying the electrical energy comprises applying the energy so as to modify a sensation perceived by the subject.

71. A method according to claim 70, wherein applying the electrical energy comprises applying the energy so as to reduce a sensation of pain perceived by the subject.

72. A method according to claim 71, wherein applying the electrical energy comprises applying the energy so as to reduce a sensation of acute pain perceived by the subject.

73. A method according to claim 71, wherein applying the electrical energy comprises applying the energy so as to reduce a sensation of chronic pain perceived by the subject.

74. A method according to claim 71, wherein applying the electrical energy comprises applying the energy so as to reduce pain associated with a defibrillation procedure.

75. A method according to claim 71, wherein applying the electrical energy comprises applying the energy so as to reduce pain associated with a surgical procedure.

76. A method according to claim 75, wherein applying the electrical energy comprises applying the energy so as to allow a reduction of a quantity of anesthesia normally associated with the surgical procedure.

77. A method according to any one of claims 56-64, and comprising applying a pacing signal to the nervous tissue, responsive to the sensing.

78. A method according to claim 77, wherein applying the pacing signal comprises sensing the action potential in the tissue and pacing the tissue responsive to the sensing, and wherein applying electrical energy to the nervous tissue to inhibit the propagation comprises applying energy to inhibit propagation of an action potential after the tissue is paced.

79. A method according to claim 78, and comprising sensing further electrical activity of the tissue after applying the energy to inhibit the propagation, in order to verify that inhibition has taken place.

80. A method for modulating a characteristic of muscle tissue of a human subject, comprising:

applying inhibitory electrical energy to nervous tissue of the subject, so as to inhibit propagation of an action potential in the nervous tissue; and

applying a pacing signal to the nervous tissue, so as to modulate the characteristic of the muscle tissue.

81. A method according to claim 80, wherein applying the electrical energy and applying the pacing signal modulate dysfunctional contraction of the muscle tissue.

82. A method according to claim 80 or claim 81, and comprising sensing a first plurality of action potentials having a first rate, wherein applying the inhibitory electrical energy comprises applying the inhibitory electrical energy so as to inhibit the first plurality of action potentials, and wherein applying the pacing signal comprises applying the pacing signal so as to induce propagation of a second plurality of action potentials having a second rate.

83. A method according to claim 82, wherein applying the pacing signal comprises applying the pacing signal such that the second rate is higher than the first rate.

84. A method according to claim 82, wherein applying the pacing signal comprises applying the pacing signal such that the second rate is lower than the first rate.

85. A method for controlling epilepsy in a human subject, comprising applying electrical energy to a portion of a brain of the subject to inhibit propagation therein of an action potential related to the epilepsy, so as to control the epilepsy.

86. A method according to claim 85, wherein applying the electrical energy comprises injecting current so as to induce anodal block.

87. A method according to claim 85, wherein applying the electrical energy comprises configuring the electrical energy so as to substantially not cause generation of an action potential in at least a sub-portion of the portion of the brain.

88. A method according to claim 85, and comprising sensing electrical activity of the portion of the brain and setting a parameter of the application of the energy responsive to the sensed electrical activity.

89. A method according to any one of claims 85-88, and comprising applying a pacing signal to the portion of the brain.

90. A method for modulating an output of a nerve cell in a human subject, comprising applying electrical energy to the nerve cell so as to modulate an output frequency thereof.

91. A method according to claim 90, wherein applying the electrical energy comprises applying electrical energy including a blocking component, so as to inhibit an action potential from stimulating the nerve cell.

92. A method according to claim 90, wherein applying the electrical energy comprises applying the electrical energy so as to modify a breathing rate of the subject.

93. A method according to claim 90, wherein applying the electrical energy comprises applying the electrical energy so as to modify a heart rate of the subject.

94. A method according to claim 90, wherein applying the electrical energy comprises configuring the electrical energy so as to substantially not cause generation of an action potential in a vicinity of the nerve cell.

95. A method according to claim 90, and comprising sensing electrical activity of the nerve cell and setting a parameter of the application of the energy responsive to the sensed electrical activity.

96. A method according to any one of claims 90-95, and comprising applying a pacing signal to the nerve cell.

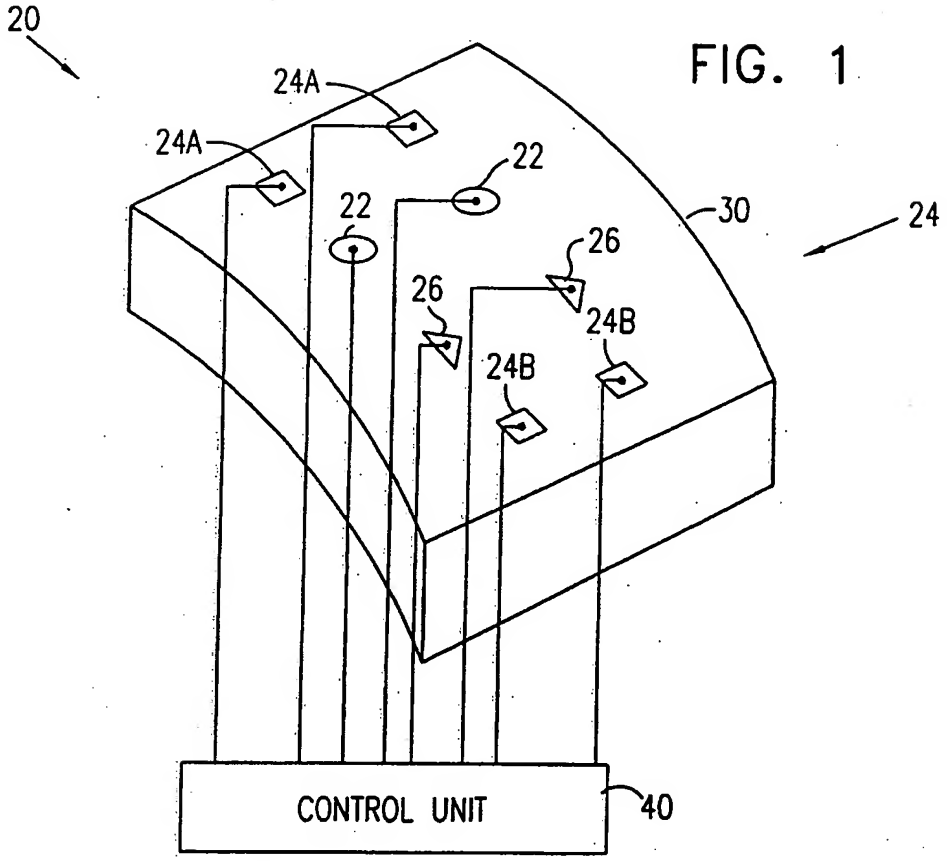

20
24A
24A
22
22
30
24
26
26
24B
24B
CONTROL UNIT
40

FIG. 1

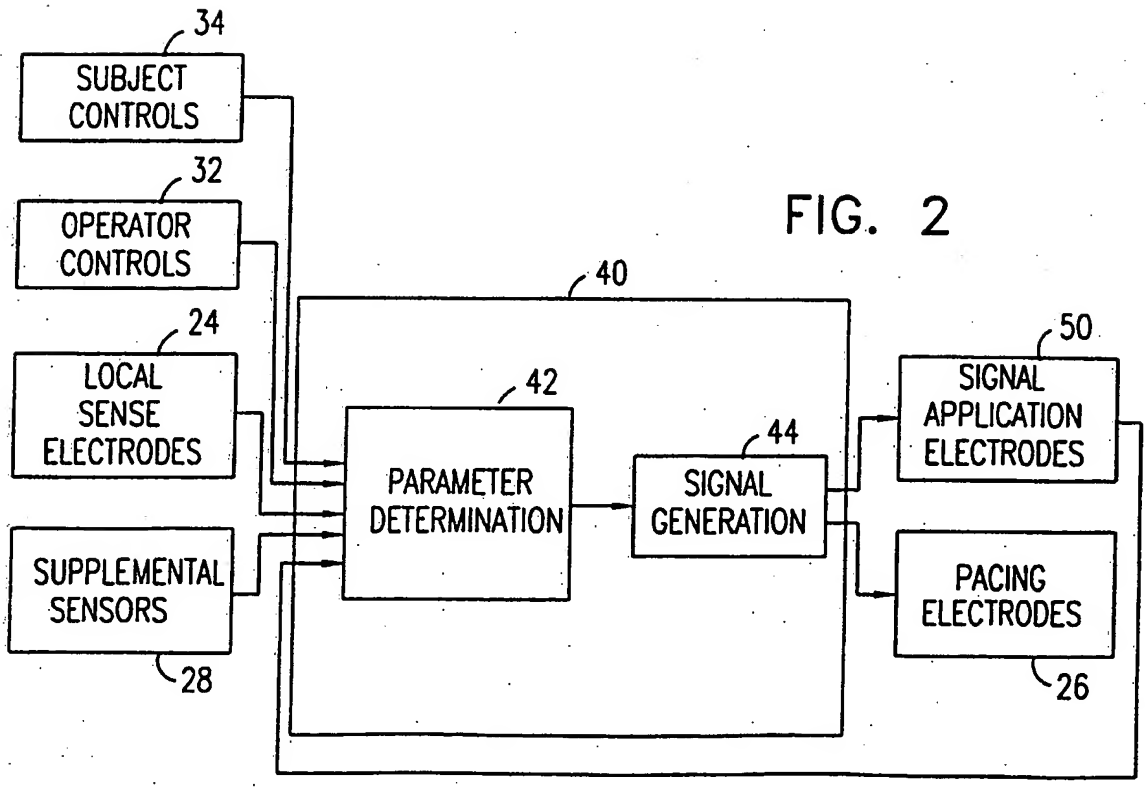

34
SUBJECT CONTROLS
32
OPERATOR CONTROLS
24
LOCAL SENSE ELECTRODES
SUPPLEMENTAL SENSORS
28
40
42
PARAMETER DETERMINATION
44
SIGNAL GENERATION
50
SIGNAL APPLICATION ELECTRODES
PACING ELECTRODES
26

FIG. 2

FIG. 3

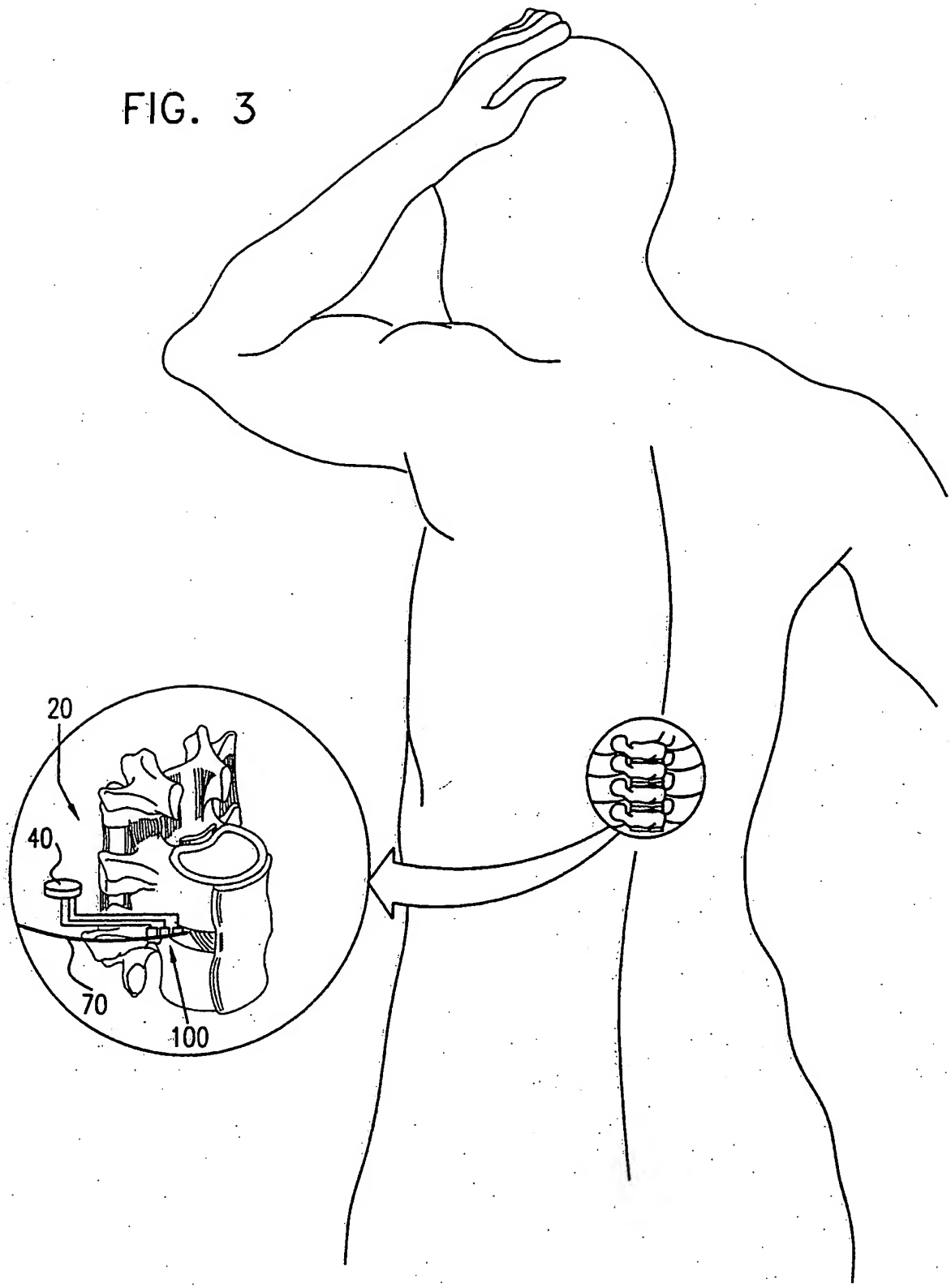
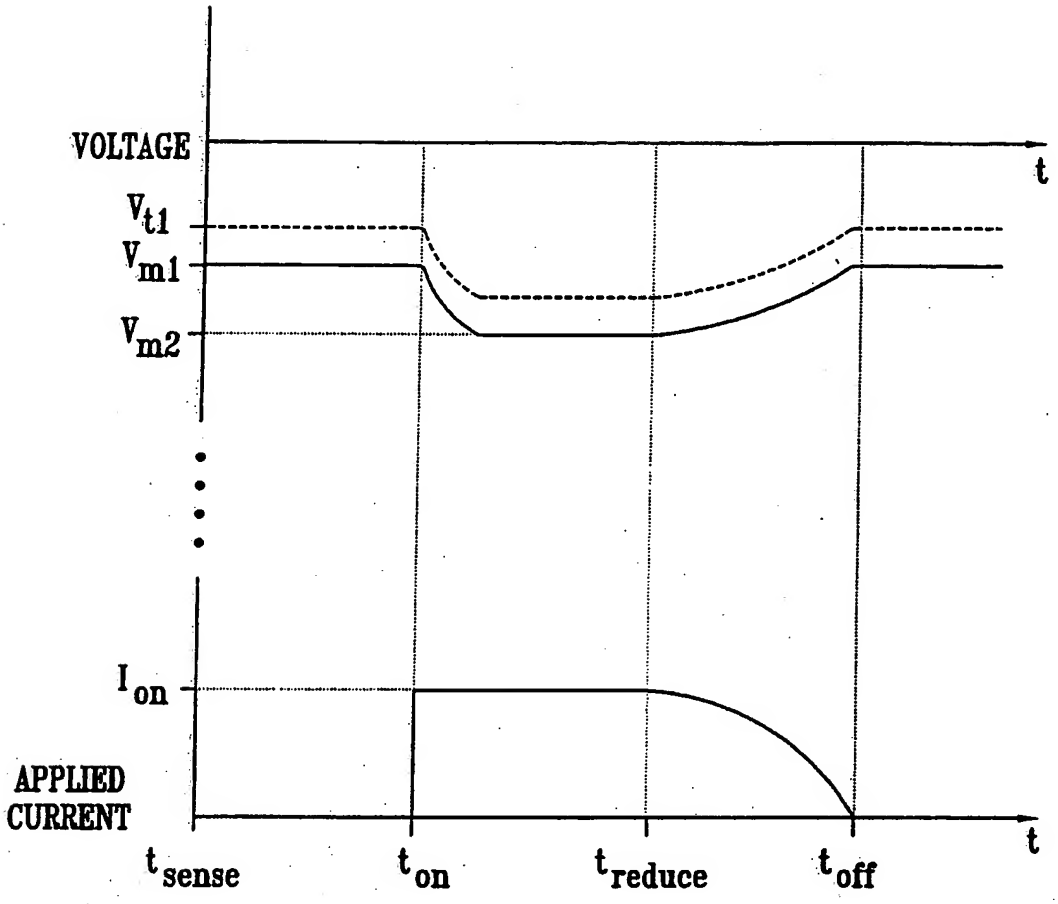


FIG. 4


VOLTAGE
t
$V_{t1}$
$V_{m1}$
$V_{m2}$
$I_{on}$
APPLIED CURRENT
t
$t_{sense}$
$t_{on}$
$t_{reduce}$
$t_{off}$

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10375 A3

(51) International Patent Classification[7]: A61N 1/34

(21) International Application Number: PCT/IL00/00467

(22) International Filing Date: 3 August 2000 (03.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/368,124 4 August 1999 (04.08.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/368,124 (CIP)
Filed on 4 August 1999 (04.08.1999)

(71) Applicant *(for all designated States except US)*: IMPULSE DYNAMICS NV [NL/NL]; 3 L.B. Smithplein, Curacao (AN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: FELSEN, Bella [IL/IL]; Hatzvi Street 26, 34355 Haifa (IL). DARVISH, Nissim [IL/IL]; Hantke Street 22A, 34606 Haifa (IL). GOLDENHOLZ, Daniel [US/US]; 2231 W. Glenbrook Lane, Mequon, WI 53092 (US).

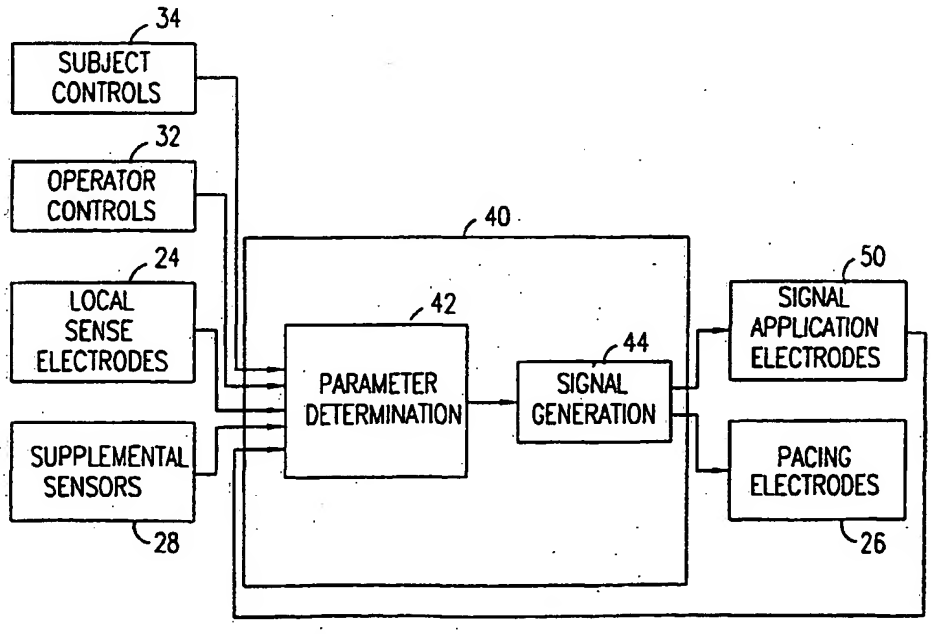
(74) Agents: COLB, Sanford, T. et al.; Sanford T. Colb & Co., P.O. Box 2273, 76122 Rehovot (IL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,

*[Continued on next page]*

(54) Title: INHIBITION OF ACTION POTENTIALS




(57) Abstract: Apparatus (20) for modifying the electrical behavior of nervous tissue (30) in a human subject is provided. At least one inhibiting electrode (22) is placed in a vicinity of the subject's nervous tissue, and a control unit (40) drives the at least one inhibiting electrode to apply electrical energy to the nervous tissue to inhibit propagation therein of an action potential. Preferably, application of the electrical energy substantially does not cause generation of an action potential in at least a portion of the nervous tissue.

WO 01/10375 A3

IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

**(88) Date of publication of the international search report:**
16 August 2001

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 00/00467

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N1/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5 716 377 A (KING GARY W ET AL)<br>10 February 1998 (1998-02-10) | 1,2,7,8,<br>11,<br>14-18,21 |
| Y | the whole document | 3-6,9,<br>10,19,<br>20,23-26 |
| A | | 12,13,<br>22,27-34 |
| | --- | |
| X | US 5 702 429 A (KING GARY WILLIAM)<br>30 December 1997 (1997-12-30) | 1,2,7,8,<br>11,<br>14-18,21 |
| Y | the whole document | 19,20,<br>23-26 |
| A | | 3-6,9,<br>10,12,<br>13,21,<br>22,27-34 |
| | --- | |
| | -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 November 2000 | 20. 03. 2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Allen, E |

1

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 00/00467

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5 792 186 A (RISE MARK T)<br>11 August 1998 (1998-08-11)<br>cited in the application | 1,2,7,8,<br>11,<br>14-18,21 |
| A | the whole document | 3-6,9,<br>10,12,<br>13,19,<br>20,22-34 |
| | --- | |
| Y | US 4 608 985 A (CRISH TIMOTHY J ET AL)<br>2 September 1986 (1986-09-02) | 3,4 |
| A | the whole document | 1,2,5-34 |
| | --- | |
| Y | WO 99 03533 A (FENSTER MAIER ;BEN HAIM SHLOMO (IL); DARVISH NISSIM (IL); FELZEN B) 28 January 1999 (1999-01-28) | 5,6 |
| A | page 20-21 | 1-4,7-34 |
| | --- | |
| Y | US 5 330 515 A (RUTECKI PAUL ET AL)<br>19 July 1994 (1994-07-19)<br>column 6-13 | 9,10 |
| | --- | |
| A | US 5 178 161 A (KOVACS GREGORY T A)<br>12 January 1993 (1993-01-12)<br>column 2-11 | 1-34 |
| | --- | |
| A | US 5 755 750 A (JOHNSON RICHARD D ET AL)<br>26 May 1998 (1998-05-26)<br>cited in the application<br>the whole document | 1,11-13 |
| | ----- | |

1

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 00/00467

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 56-96
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-34

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-34

   Apparatus for modifying electrical behaviour of nerve tissue by inhibition of action potentials using direct current

2. Claims: 35-39

   Apparatus for controlling epilepsy

3. Claims: 40-47

   Apparatus for modulating an output frequency of a nerve cell

4. Claims: 48-55

   Apparatus for modulating a characteristic of muscle tissue

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IL 00/00467

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 5716377 A | 10-02-1998 | AU 2606097 A | 12-11-1997 |
| | | EP 0959942 A | 01-12-1999 |
| | | WO 9739796 A | 30-10-1997 |
| | | US 5833709 A | 10-11-1998 |
| US 5702429 A | 30-12-1997 | US 5913882 A | 22-06-1999 |
| | | US 5814092 A | 29-09-1998 |
| US 5792186 A | 11-08-1998 | US 5683422 A | 04-11-1997 |
| | | AU 2595397 A | 12-11-1997 |
| | | EP 0895483 A | 10-02-1999 |
| | | WO 9739795 A | 30-10-1997 |
| US 4608985 A | 02-09-1986 | NONE | |
| WO 9903533 A | 28-01-1999 | AU 3458197 A | 10-02-1999 |
| | | EP 0996482 A | 03-05-2000 |
| US 5330515 A | 19-07-1994 | AU 4641493 A | 04-01-1994 |
| | | JP 8500988 T | 06-02-1996 |
| | | WO 9325271 A | 23-12-1993 |
| US 5178161 A | 12-01-1993 | US 5314495 A | 24-05-1994 |
| US 5755750 A | 26-05-1998 | NONE | |